CLINICAL PROCEEDINGS

of the

CHILDREN'S HOSPITAL

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CLINICAL PROCEEDINGS

OF THE CHILDREN'S HOSPITAL

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TETANY IN NEWBORN SIBLINGS

James Stallings, M.D.
Frederic G. Burke, M.D.
John A Washington, M.D.

CASE REPORTS*

CASE #1: B. G., A 9 day old white male, was admitted on August 8, 1952, because of convulsive movements.

He was born at Garfield Hospital after an uncomplicated delivery, weighing 6 lbs. 12 oz. While in the hospital, his mother noticed a few fine twitching movements of the extremities, which the nurses did not observe. The infant seemed pale and lethargic and took feeding poorly. Subsequently the evaporated milk formula was changed to similac 1:1, with 1.5 gms. calcium lactate added to each bottle, which was taken reluctantly. There were no further episodes of twitching or carpopedal spasm, and the patient was discharged in apparently good condition on August 10, 1952.

He was readmitted on September 3, because of recurrent twitching movements of one day's duration. He had done well at home until one week prior to the second admission, when because of vomiting he was changed from a Similac formula to Lactum. On the day of admission, the parents noticed twitching on the left side of the body. On examination, he was afebrile, weighed 8 lbs. 5 oz., and appeared to be in no distress. Neurological examination was entirely normal. (He had been given ¾ gr. of sodium luminal, intramuscularly, one hour before hospitalization.)

Serum calcium on this admission was 6.8 and phosphorus was 9.8 milligrams per cent. One gram of calcium chloride was given by gavage one hour after admission. Fasting capillary blood sugar was 50 milligrams per cent and blood urea nitrogen was 13.7 milligrams per cent. X-ray of the long bones showed transverse zones of decreased densities in the metaphyses possibly indicating poor mineralization. No ossification centers were present in the carpal region.

Hospital course was uneventful except for some loose stools and mild dehydration on the third hospital day, treated with clyses and Terramycin. The baby was discharged on September 6, and is said to have done well at home.

Case #2: R.G., a sibling of B.G., was born on June 28, 1953 at Garfield Hospital, was admitted to this hospital on July 6, 1953, because of generalized twitching (predominently left-sided) which was partially controlled with intramuscular barbiturates.

He was born at term, after an uneventful pregnancy and delivery, and did well until the day of admission, when he had a clonic seizure accompanied by cyanosis, and the private physician was called and gave luminal. On admission to Children's Hospital he occasionally exhibited carpopedal spasm and a positive Chvostek's sign, but examination was otherwise normal. Serum calcium, drawn on admission, was 7.8 and phosphorus was 9.8 milligrams per cent. During gavage with calcium chloride, he had another clonic seizure followed by cyanosis, and was placed in oxygen. He was gavaged again with 1 gram of calcium chloride six hours later, and displayed no more twitchings or seizures. One gram of calcium gluconate was added to each bottle of formula, which was taken well with no vomiting. He was discharged in good condition on July 8, 1953.

* Private patients of Bennett Olshaker, M.D.

DISCUSSION

John A. Washington, M.D.

In reviewing tetany, generally it is worth pointing out that the classical form of the disease has practically disappeared because of wide distribution of vitamin D preparation and, probably more important, because of inclusion of vitamin D in evaporated milk, the cheapest sort of milk for infant feeding. A baby now gets vitamin D whether or not his mother has sense enough to give it to him. The classical form of tetany occurred of course with rickets. The signs included carpopedal spasm and sometimes spasm of the facial muscles causing an expressionless, drawn appearance. Laryngospasm of serious degree occasionally appeared as well as generalized convulsions. Positive Chvostek, Trousseau, and Erb signs were present with some regularity. A plausible explanation for the production of this form of tetany is as follows: with a deficit of vitamin D, absorption of calcium and phosphorus from the intestine fails to take place. To prevent a subsequent drop in the serum calcium, the parathyroid glands hypertrophy with a resultant over-production of parathormone which maintains the serum calcium at a normal level. Phosphorus, on the other hand, is not retained as the excess parathyroid hormone encourages its excretion through the kidneys. At this stage rickets exist, the growing bones being deprived on their normal supply of calcium and phosphorus, the serum calcium level being reduced. Tetany develops when this mechanism breaks down so that the serum calcium level drops. This accident rarely happens.

With classical tetany practically wiped out, the most usual form of tetany seen today is "neonatal tetany". The two cases presented are unusual examples. Talbot describes this disease as a "semi-pathological condition." I doubt if the pediatrician who had charge of these particular cases regards the disease as being as benign as this description implies. Neonatal tetany occurs usually in the first week of life. It can appear on the first day and has been reliably reported as late as the eighth week. Serum calcium levels are low and phosphorus levels high. The cause is assumed to be a functional inadequacy of the parathyroid glands. These glands in the fetus are not called upon to regulate calcium and phosphorus, the regulation already accomplished in the mother's serum so that proper proportions are delivered across the placental barrier. There is some evidence that the parathyroid hormone itself cannot cross this barrier. After birth these unpracticed parathyroid glands occasionally fail for a time to produce TS hormone in adequate quantity and tetany results. Babies fed cow's milk ingest a much higher proportion of phosphorus. An ordinary day's formula might contain 1600 mgm. of phosphorus in contrast to 300 mgm. in an equivalent quantity of breast milk. Inefficient parathroid glands are

simply unable to stimulate the kidneys (not too mature themselves) to discard all of this phosphorus and the calcium level see-saws down.

On newborn wards tetany manifests itself usually by convulsions. Carpopedal spasm is not so characteristic as in classical tetany. A positive Chvostek sign is unreliable at this early age. Differentiating between tetany and cerebral disturbance due to hemorrhage, anoxia or agenesis may be impossible. Determinations of serum calcium and phosphorus levels if obtainable require time for completion. One often elects to treat for tetany with the attitude that such treatment will do not harm if tetany does not exist and also that the results of treatment may aid in the differential diagnosis. Since intramuscular calcium may cause severe sloughing, two routes of administration remain. If a pediatric small vein virtuoso is on hand, five or ten c.c. of 10 per cent calcium gluconate intravenously will end tetanic convulsions. The other route is via the intestinal tract. Here calcium chloride is the drug of choice initially because it produces an acidosis which in moderation is an advantage. Three one-gram doses (½ gram in small babies) during the first 24 hours are sufficient to control the convulsive state. The surest way to get calcium chloride into the newborn is by gavage. If too many doses are given, a harmful acidosis may result. If given in too concentrated a form, damage to the stomach wall has been reported. A 2 per cent solution is safe.

After controlling acute tetany by either of these methods, calcium in the form of calcium lactate should be given for two weeks, one gram three times a day. At the end of this time, in practically all instances the parathyroid glands are capable of controlling the situation. One further precaution is advisable in bottle fed babies, namely to continue with a formula containing a higher calcium/phosphorus ratio than that which is present in ordinary cow's milk.

It is apparent that the two cases presented today are not ordinary ones both because of their prolonged courses and because of the familial incidence. The first baby required four months of calcium therapy before regulating himself. It is interesting that on one occasion a recurrent convulsion coincided with changing the formula from Similac, with its high calcium/phosphorus ratio, to evaporated milk.

Interest in these two cases was greatly heightened by a report in the March 1954 issue of Pediatrics. It presents two successive babies in a family who were severely affected with tetany just as were our cases. This suggested to the author that the mother might be suffering from hyperparathyroidism, and investigations showed that she was. Her serum calcium was as high as 14.5 milligrams and phosphorus as low as two milligrams per cent. X-rays of the mother revealed renal lithiasis. A tumor of one parathyroid gland was removed with recovery. Investigation of

the mother of our cases showed nothing comparable to this. The calcium was very slightly elevated and phosphorus slightly depressed. X-rays show no calcification in the kidney area. Also our mother is in excellent health. If she becomes pregnant again, her blood chemistry will bear careful watching. The explanation for the severe neonatal tetany which several times has been reported to accompany maternal hyperparathyroidism probably is that the activity of the fetal parathyroid gland has been very thoroughly depressed by the high calcium and low phosphorous levels transmitted from maternal to fetal blood.

Several other forms of tetany should be mentioned. The accidental surgical removal of the parathyroid glands has been known to occur. Also Wilkins reports several cases of hypoparathyroidism due to idiopathic degeneration of the glands. A more common type is that which occurs when some form of alkalosis reduces the amount of ionized calcium in the serum below a critical level. Ordinarily 60 per cent of the serum calcium is in the ionized form. Forced breathing in encephalitis may blow off CO_2 and is known to cause it. A related form appears occasionally in babies being treated for acidosis. As they recover, tetany occurs, not because they have been pushed into alkalosis, but apparently because of the sudden shift toward alkalosis, and a reduction of ionized serum calcium. The inclusion of calcium gluconate in the intravenous fluids is a fairly common practice as a precaution against this accident. Finally, tetany occurs in chronic nephritis where the excretion of phosphorous by the kidney is depressed. As the serum phosphorus rises the serum calcium see-saws downward and convulsions suddenly appear.

Frederic G. Burke, M.D.

A review of the roentgenograms that we have on the mother of these siblings including films of the chest, thorax, abdomen and pelvis revealed nothing really remarkable. There is perhaps a slight demineralization of the long bones but nothing that gives specific evidence of a definite calcium-phosphorous abnormality or any abnormality of parathyroid function. There is no evidence to be found in the flat plate of the abdomen of renal calcification. The expirational film does show the liver to descend several inches below the 11th rib, but on inspiration the liver is noted to be of normal size. I must regard these films as being within the normal range.

The X-rays on the first child at the age of six weeks revealed transverse bands of increased density in the metaphyses, most marked in the radius and probably representing a temporary period of retarded development in this early period of life. Transverse lines which form shortly after birth may be caused by the deposition of bone when the source of nutrition shifts from the placenta to the infant's intestine. Almost any disease which

produces arrest in growth is capable of altering the architectural factors in the active growth centers of infant's bone, producing such transverse lines of increased density. The bones most commonly affected are the radius, ulna, tibia and femur which represent the sites of the most rapid growth in early life. There is, in addition in these films, some demineralization of the shafts and in view of these transverse zones of increased density, it may be concluded that these are evidences of a disturbance in the calcium deposition of this infant.

THE THERAPY OF TETANUS

William Oberman, M.D.

With present day methods of widespread production of active and passive immunity with tetanus toxoid and antitoxin, the incidence of tetanus has been materially reduced. However, despite better understanding of the pathologic physiology of the disease, in the past few years little progress has been made in the therapy of tetanus once the disease has become established, and clinical tetanus remains a frequently fatal disease.

CASE REPORT

M. S., an 11 year old white female was admitted to Children's Hospital on June 30, 1954 with the history of mangling the third, fourth, and fifth toes of her left foot in bicycle spokes 10 days prior to admission. She was immediately taken to a local hospital and her wound was sutured. Three days later (one week prior to admission) she returned to the hospital when the fourth left toe was found to be gangrenous and was amputated. At that time 0.5cc of tetanus toxoid and 600,000 units of procaine penicillin were administered. She had been primarily immunized with triple vaccine (DPT) at age six and the booster dose of toxoid was thought to be sufficient. Five days prior to admission (and five days following the injury) she was again seen by her private physician and given another 600,000 units of procaine penicillin. On that day it was first noted that she had difficulty opening her mouth. The following day she received 10,000 units of tetanus antitoxin intramuscularly. Three days prior to admission definite muscle rigidity was noted. Her wound was irrigated and some of the sutures were removed.

She was placed on bicillin 300,000 units every eight hours and was give pyribenzamine for an urticarial reaction supposedly due to the tetanus antitoxin. Later that day, muscle spasms were first noted and these increased in severity and frequency until admission to the hospital. There had been no convulsions.

Physical examination on admission revealed a well developed, well nourished white female with obvious trismus and mild opisthotonus. Her rectal temperature was 101.4°. Severeral generalized muscle spasms occurred on slight stimulation. There was an obviously macerated infected wound on the left foot. The fourth left toe was absent. The remainder of the physical examination was within normal limits.

A presumptive diagnosis of tetanus was made and therapy was started immediately

on admission. She was placed in a quiet darkened room and the number of persons entering the room was restricted. A continuous intravenous drip was started to which 500 mg. of intravenous achromycin was added every six hours. She was placed in an oxygen tent and her excess oral secretions were repeatedly suctioned. Sedation with rectal avertin was attempted but the patient repeatedly expelled this medication. Consequently sedation was maintained with repeated small doses of intravenous nembutal. In addition, a muscle relaxant, "anectine" (succinylcholine) was administered by slow intravenous drip as a 0.1 per cent solution. The rate of administration was governed by gauging the rigidity of the patient's abdominal muscles. Tetanus antitoxin in a total dose of 100,000 units was administered. Because of an urticarial reaction to the antitoxin, it was initially given in small amounts of 1/1000 dilution gradually increasing through 1/100 and 1/10 dilution to full strength. Intravenous benadryl was given to control the urticarial reaction. Locally, the wound was opened widely but not debrided and continuous aluminum subacetate soaks were applied. The patient was catheterized for urinary retention.

The day following admission, the patient was fairly well sedated and had infrequent mild spasms. Hydration was maintained by intravenous fluids. On the third hospital day an attempt was made to pass a polyethylene catheter through the nose in order to gavage feed. During the procedure the patient had a severe generalized spasm with concurrent laryngospasm and stopped breathing. An emergency tracheotomy was performed but during the latter stage of this operation, cardiac standstill supervened. Intracardiac adrenaline and intravenous coramine resulted in a resumption of the heartbeat after a total period of five minutes. Artificial respiration was administered and the child began breathing regularly after a total apneic period of 40 minutes.

Following resuscitation, large quantities of tracheal secretions were produced requiring almost constant tracheal aspiration. With return of muscle spasms, intravenous nembutal was again given for sedation but proved unsatisfactory so that rectal avertin in a dose of 50 mg. per kilogram of body weight was administered. Sedation was quite satisfactory and repeat doses of 30 mg. per kilogram of body weight were necessary at about six hour intervals.

On the fourth hospital day the child was well sedated and having minimal muscle spasms. Intravenous fluids were continued. The urinary output was excellent and the blood electrolyte pattern was normal. Penicillin (1,000,000 units intramuscularly every six hours) was added to the therapeutic regime. The amount of tracheal secretions gradually diminished and her lungs seemed to be aerating fairly well. Her axillary temperature ranged from 101°–104°. Her condition was satisfactory until without warning she became apneic. All attempts at restarting respiration failed and she expired one hour later.

Autopsy revealed pulmonary edema and congestion bilaterally. Microscopically, an acute meningitis was noted over both cerebral hemispheres.

PATHOLOGIC PHYSIOLOGY OF TETANUS

Tetanus is caused by the bacterial organism clostridium tetani, a gram positive, spore forming rod. This organism is widely distributed through nature especially where there has been contamination with feces of domestic animals. Organisms have been found in soil, street dust, mud, fresh and salt water, gun wads, and wearing apparel. The organism gains entrance to the body through a wound contaminated by soil or clothing following bullet

wounds, puncture wounds, contused wounds or compound fractures. Other sources of infection include splinters, induced abortions, vaccination sites, horse serum or gelatin injections, surgical operations, burns, and tooth extractions. The wound may be insignificant and be completely missed in a routine physical examination. If a wound is clean and all devitalized tissue removed at the time of the accident, the chance of developing tetanus is small since the organism requires a low oxygen tension, such as is present in necrotic areas, to germinate and grow.

Under favorable circumstances, the organisms multiply rapidly at the wound site but remain localized and do not enter the blood stream. They, however, manufacture a very virulent neurotoxin and it is from the effects of this neurotoxin that the symptoms of tetanus arise. There is argument as to how this powerful neurotoxin reaches the central nervous system, some authorities believing that it ascends via the axis cylinders of the nerves and thence up the spinal cord (2), others feeling that the toxin reaches the central nervous system via the blood stream (3). In any event, the toxin becomes fixed to the ganglion cells of the anterior horn and cranial nerve motor nuclei causing them to become hypersensitive to minimal stimuli and resulting in the reflex convulsive activity so typical of tetanus. This neurotoxin becomes so firmly fixed to the nerve tissue that dissociation is impossible. This fixed toxin is thought to be unaffected by circulating antitoxin which can neutralize only the circulating toxin leading some investigators (4) to state that once a lethal dose of tetanus toxin is fixed to the nerve cells, the prognosis is hopeless. A secondary action of tetanus toxin is a peripheral one exerted on the neuromuscular junction resulting in generalized persistent muscular rigidity (1).

Sublethal doses of toxin supposedly run a variable course and it is in these cases of tetanus that the full resources of the physician are called into play to cope with respiratory infection and obstruction, exhaustion, and disturbances in nutrition and fluid balance. Even in the most severely ill patients, if treatment results in recovery, there are no residuals.

THERAPY OF TETANUS

In evaluating any therapeutic regime it is necessary to grade the severity of the attack. Many patients with severe tetanus will die despite any and all heroic measures; others with mild tetanus will recover with or without any or minimal treatment. But it is the large intermediate group which may go one way or the other that warrants full and intensive therapy.

An attempt has been made to grade the severity of the attack by certain criteria. The two criteria that have been found most valuable in this respect are (A) the incubation period—the period elapsing between the time of injury and the first appearance of muscle rigidity and (B) the period of

onset—the time elapsing between the onset of rigidity and the onset of the first reflex spasm. It is felt that if (A) is less than seven days or (B) less than two days the prognosis is bad and if (A) and (B) is less than seven days the prognosis is hopeless despite all therapy (5). Recent literature casts some doubt on the validity of this observation.

The causes of death in tetanus are many and varied but principally consist of mechanical obstruction of the respiratory tract by secretions, spasm leading to asphyxia, exhaustion associated with infection, and serum reactions (5).

The basic treatment of tetanus is to prevent extension of the disease and neutralize the toxins already present. Rigidity and muscle spasm must be controlled in order to prevent death due to exhaustion, and pulmonary function and nutrition must be maintained. These basic principles will be outlined below.

(A) *Prevention of the further absorption and neutralization of the absorbed tetanus antitoxin*

(1). Prophylaxis: There is no natural immunity to tetanus and since tetanus toxin is only feebly antigenic, natural immunity is not acquired even following the disease (1). Under such circumstances the wisdom of early active immunization is obvious. The practice of active immunization against tetanus has become widespread and represents the chief reason for the decreased incidence of tetanus. Infants even under the age of three months are capable of developing antibodies against tetanus so that active immunization is recommended within the first six months of life.

Alum precipitated tetanus toxoid is administered in amounts of 0.5–1.0 cc intramuscularly or subcutaneously at monthly intervals for a total of three doses. A booster dose of 0.5 cc should be given one year after immunization and repeated every two years (1) (6). If for any reason the second or third injection is missed, it may be given as long as nine months later with excellent antibody response. A booster dose will produce protective levels by the end of one week, and booster doses given as long as 10 years after the primary immunization will produce adequate levels (7). Alum precipitated toxoid is felt to be superior to fluid toxoid due to the more durable immunity of the former.

(2). Treatment with tetanus toxoid at the time of injury: At the time of injury in an immunized patient, providing he has had a booster dose of tetanus within the past one–two years, no further toxoid administration need be given. In an extensively contused wound or any other lesion considered capable of harboring tetanus organisms 1 cc of the fluid toxoid should be given. Fluid toxoid has been found to raise the antitoxin level more promptly (6) than alum precipitated toxoid.

(3). Tetanus toxoid plus tetanus antitoxin: Under certain conditions it is advisable to administer both tetanus toxoid and tetanus antitoxin in an immunized individual. In cases where the wound is extensively contaminated with the probability of large quantities of tetanus toxin being elaborated, the level of circulating antitoxin from previous immunization may not be adequate. A booster dose of toxoid may not act rapidly enough or produce high enough antitoxin levels. Under such circumstances the level can be temporarily increased by administering tetanus antitoxin (6). In an immunized individual the administration of tetanus antitoxin does not interfere with the active production of tetanus antitoxin. Both toxoid and antitoxin should be given simultaneously. Other possible indications for the simultaneous administration of tetanus toxoid and antitoxin include a delay of 24 hours in giving a recall dose of toxoid, marked general debility from any number of causes (hemorrhage, etc.), and questionable history of primary immunization (7).

(4). Tetanus antitoxin: In a non-immunized individual it is imperative that tetanus antitoxin be given immediately following the occurrence of an injury considered likely to favor the growth of tetanus organisms. Spaeth (8) decries the routine use of 1500 units of prophylactic antitoxin and feels that 10,000–20,000 units of tetanus antitoxin should be used routinely for prophylaxis. He notes that 1500 units produces titratable immunity for two–three weeks while 10,000 units produces immunity for six–ten weeks and 100,000 units produces immunity for eight–eleven weeks.

Should clinical tetanus supervene, amounts of tetanus antitoxin ranging from 30,000 to 200,000 units have been advised (9). One-half should be given intravenously (1) and one half should be given intramuscularly. There is no need for further injection of antitoxin after the initial dose as the antitoxin levels produced are adequate enough to neutralize any circulating toxin and to neutralize any toxin that is subsequently elaborated.

Every patient who is a candidate for tetanus antitoxin should have a preliminary skin test for sensitivity to the product. 0.1 cc of 1/100 or 1/1000 dilution is recommended. If the patient proves sensitive to the antitoxin it is necessary to administer it in gradually increasing dilutions of 1/1000–1/100–1/10–undiluted every fifteen minutes until the total amount has been given. Intravenous or oral antihistaminics may be given concurrently if a sensitivity reaction develops. Bovine antitoxin has been recommended for passive immunization in persons with a definite history of allergy (9a).

Intrathecal tetanus antitoxin has been advised by some. Pratt (9), however, reports two cases of mild tetanus who were given intrathecal antitoxin and who subsequently died. It is felt that intrathecal administration is definitely contra-indicated.

(5). Subsequent active immunization with tetanus toxoid: One attack of tetanus does not produce lasting immunity and second infections have been known to occur. Consequently it is important that any person who has recovered from tetanus and who was given tetanus antitoxin be subsequently actively immunized against tetanus, especially since sensitivity to tetanus antitoxin if not originally present almost assuredly develops (9). Toxoid should be given at about the time that the effect of the antitoxin is diminishing (6–8 weeks in the case of 10,000 units; 8–11 weeks in the case of 100,000 units). At that time the response to toxoid is adequate; prior to that time passive immunity interferes quantitatively with the development of active immunity (8). Reactions to tetanus toxoid are extremely uncommon.

(6). Surgical debridement: There is no unaminity of opinion as to the advisability of surgical debridement of the wound after the onset of clinical tetanus. Some authorities (5), (10) routinely debride widely, others (9) feel that it is futile to debride once symptoms have appeared since adequate amounts of circulating antitoxin alone will neutralize any amounts of toxin subsequently elaborated. Following the same line of reasoning it would seem unnecessary to inject tetanus antitoxin locally into the wound, but again the local injection of 10,000 units of antitoxin has been advised by some workers in the field (4). However, all authorities agree that adequate debridement of all devitalized tissue at the time of injury is indicated as is the proper care of the wound during the disease as if the tetanus did not exist.

(7). Penicillin: Penicillin inhibits the local growth of the organisms at the site of injury. Theoretically the routine administration of intramuscular penicillin in large doses would prevent the further elaboration of toxin (1). In actual practice, penicillin has been found to exert no demonstrable effect on the clinical course of tetanus (11). Penicillin is of value, of course, in the prophylaxis and treatment of pulmonary complications of tetanus. This will be discussed in a further section.

(B) *Control of reflex spasm of muscles with sedations and relaxants*

Despite the neutralization of circulating tetanus toxin by antitoxin, the problem of the toxin already fixed to spinal cord ganglia and cranial motor nuclei remains. If the resultant muscle rigidity, muscle spasm and convulsions are not adequately controlled, the patient soon dies of exhaustion. In spite of the control of convulsions by heavy sedation, the mortality rate has remained high (10). This is probably due to respiratory depression since the margin of error between the therapeutic and toxic doses of most sedatives and relaxants is very small. Shackleton (5) notes that muscle relaxants have not really increased the chance for survival in severe and

intermediate cases of tetanus. He feels that they have in effect even hastened death in many cases due to respiratory paralysis. The problem of a satisfactory and *safe* sedative and relaxant remains with us still.

(1). Sedatives: Godman and Adriani (12) evaluated various sedatives in the therapy of tetanus. They found phenobarbital to be a good sedative but ineffective in controlling muscular rigidity and spasm. Amytal was effective in relieving spasm but did not control rigidity. They discarded intravenous procaine drip and intravenous sodium pentothal in therapy because of the need for constant attention and the danger of respiratory depression.

Avertin by rectum proved to be fairly effective in their hands and is used by many other authorities (5), (10). They found that rigidity and spasm could be controlled very well but there were varying degrees of respiratory depression. Disadvantages include an irregular absorption pattern and the development of proctitis. Avertin was given per rectum in a dose of 50 mg. per kilogram of body weight with 100 cc of distilled water. This dose could be safely repeated as needed every four to six hours.

(2). Relaxants: This group of therapeutic agents has been used in the treatment of tetanus due to their well known attribute of partially or completely paralyzing skeletal muscle. Such an action occurs peripherally at or near the myoneural junction. The motor nerves are unaffected unless large doses are given. Theoretically this means of management would be ideal but again the margin of error between therapeutic and toxic doses is uncomfortably small.

(a) Curare and curare-like derivatives: The action of these agents is to stabilize the motor end plate and prevent depolarization. This neuromuscular block is overcome by administering anti-cholinesterases (13). Curare has been found to produce excellent muscular relaxation in tetanus (5), (12), (14), but suffers from the disadvantage of a low margin of safety and too rapid loss of effect. Adriani (14) found that relief from muscle spasm was not obtained until almost to the point of complete curarization. The effect lasted from 20–30 minutes and respiratory depression and obstruction were common. Curare preparations have been pretty well abandoned by most investigators. The newer compounds in this group of relaxants, "Flaxedil" and "Mytolon" have shown promise but have been incompletely evaluated.

(b) Succinylcholine: This agent has shown great promise in controlling muscular rigidity and spasm. The site of action is also at or near the motor end plate which the drug depolarizes so that it becomes refractory to motor impulses (13). Succinylcholine differs from the other drugs in this group in that its action is markedly potentiated by anti-cholinesterases (eserine, prostigmine, TEPP). Atropine has no effect.

The chief advantage of succinylcholine is its extremely short duration of

action. There is no cumulative action or tachyphylaxis. The ganglia are unaffected until 650 times the amount that is necessary to paralyze the peripheral muscles is given. For sustained relaxation a 0.1–0.2% solution is administered by continuous intravenous drip and the degree of relaxation is regulated by adjusting the rate of infusion (5), (13). The drug is relatively free from side effects except for occasional hypertension. Respiration may also be depressed. In our experience in the use of succinylcholine by continuous intravenous drip in the case presented, we found it to be most satisfactory in controlling muscular rigidity and spasm. The rate of administration was governed so that the abdominal muscles were relaxed and we noted no respiratory depression at this level.

(c) Myanesin: This drug has found ubiquitous use in the therapy of tetanus (5), (12), (15) but differs from the other muscle relaxants in that its site of action is the central nervous system. Its exact site of action is unknown but is probably on the facilitory and inhibitory systems (13). It has proved quite satisfactory in mild and moderately severe cases of tetanus. It is rapidly detoxified by the liver. Myanesin can be used very satisfactorily in a continuous intravenous drip of 1% solution (13). Higher concentrations may cause thrombophlebitis, hemoglobinemia and hemoglobinuria. Mephenesin has been given concurrently with succinylcholine or avertin with good results (5); it has also been administered orally by stomach tube in mild cases in total doses of 62.5–750 mg. in children and up to 3500 mg. in adults together with phenobarbital or another sedative (12); it has also been administered in a continuous infusion with sodium pentothal in a mixture containing 1.0 gm of myanesin and 0.75 gm of sodium pentothal in 600 ml of infusion. 60 cc per hour were given to an 11 year old child and this dose was maintained for 20 days (15).

These drugs are all useful in controlling the moderately severe case of tetanus. Frequently the muscle spasm will never become completely controlled but the degree of control is sufficient enough to prevent exhaustion of the patient. For the severe case, however, nothing will suffice short of production of a flaccid paralysis and maintenance of respiration by artificial means.

It will be realized that no therapeutic regime in tetanus can be successful without immediate consultation and cooperation with the anesthesia department. Such a liaison should be set up on the admission of the patient to the hospital and a qualified anesthesiologist should have an integral part in planning and maintaining adequate sedative and relaxant therapy.

Of great importance in reducing the number of muscular spasms in a patient with tetanus is the often-repeated but frequently ignored rule to place the patient in a quiet darkened room where stimuli are kept to a minimum. The number of visiting physicians and nurses should be sharply

restricted. Despite this, medical curiosity is great and the patient's room frequently has as much traffic going in and out as a railroad station.

(C) *Prevention of intercurrent respiratory obstruction and infection*

Sedatives and relaxants if successful in tetanus therapy must frequently be maintained for a duration of 10 to 20 days in severe cases. The problem then remains one of proper pulmonary aeration and the maintenance of respiration. *The high incidence of respiratory complications is chiefly responsible for the fatal outcome in a patient with tetanus.*

(1) Nursing care: No severe case of tetanus can be expected to recover without 24 hour a day care by an experienced nursing staff. It is the nurse who accepts the duty of suctioning when necessary, proper positioning, maintaining sedation, and immediately notifying the resident or staff physician when impending complications are about to develop.

(2) General care: Oxygen should be available if it be indicated for dyspnea and cyanosis. Oxygen may be given by tent or nasal catheter. The former method although complicating nursing care to some extent serves to keep the patient cool and discourages unnecessary handling. The latter method is equally efficient and permits more freedom of action. However, the irritating effect of the catheter in the posterior pharynx may be a contra-indication. The patient should be placed in a Trendelenberg position in order to facilitate aspiration of oral and respiratory tract fluids, and should be rotated from side to side frequently. This had best be done immediately following administration of sedation so that no muscular spasms will be initiated. A resuscitator or a means of artificial respiration should be present at the bedside; if a tracheotomy is not performed on admission a complete tracheotomy tray should also be present at the bedside. In anticipation of respiratory paralysis a complete tray of stimulants and drug antagonists should be made immediately available.

(3) Tracheotomy: Opinion differs widely on the indications for tracheotomy in tetanus. Some writers (10) advise tracheotomy on admission to the hospital if there is any evidence of oral difficulty such as trismus or dysphagia; others (1) use as their criteria uncontrollable spasms of the glottis with resultant cyanosis and asphyxia. Certainly if oral suction is inadequate and produces repeated muscular spasms, tracheotomy would seem to be indicated. Tracheotomy permits adequate aspiration of bronchial secretions in a patient who is heavily sedated. Herzon et al (16) presented their indications for tracheotomy as follows: (a) spasms of respiratory muscles; (b) absence of cough and swallow reflexes; (c) laryngeal obstruction; (d) excess bronchial secretions; (e) trauma of the tongue; (f) coma.

(4) Maintenance of respiration: For the severe case of tetanus who must have prolonged heavy sedation in order to control muscle spasms, the

prognosis is poor. The patient frequently dies of respiratory paralysis resulting from too heavy sedation. By applying methods recently used in the treatment of poliomyelitis with respiratory paralysis, however, some of these formerly hopeless cases have been saved. The tank respirator has been used to maintain respirations and has been lifesaving in some instances. It has the disadvantage of making nursing care far more complicated and the administration of sedatives difficult. Prior to placement in a respirator the patient should have a tracheotomy in order that tracheobronchial secretions may be satisfactorily aspirated. The danger of carbon dioxide retention with further respiratory depression must be kept in mind (5). Oxygen should be administered carefully to prevent the clinical picture of the hypoventilation syndrome from developing (17).

Where excess pulmonary secretions have made the use of the tank respirator impractical and dangerous a combination of tracheotomy and positive pressure inflation through the tracheotomy tube has proved lifesaving (5). The pulmonary secretions are aspirated frequently through the tracheotomy. At all other times an oxygen and nitrogen mixture is administered through an inhalation anesthesia apparatus with the rapidity of respiration being governed by pressure on the rebreathing bag. Excess carbon dioxide is absorbed by sodalime. Constant supervision of the breathing apparatus is necessary but by heroic efforts the patient may survive.

(5) Prophylactic antibiotics: For the prophylaxis of the respiratory infection which is almost certain to occur with severe tetanus large doses of antibiotics are indicated. These should be started on the day of admission. Penicillin is quite useful, although the irritation of the injection with resultant initiation of muscular spasm is to be avoided. Broad spectrum antibiotics given by the intravenous route would seem to be the drugs of choice.

(D) *Management of nutrition, and fluid and electrolyte balance*

Nutrition in a patient with an exhausting disease such as tetanus becomes of cardinal importance. Mild cases of tetanus with miminal sedation will take oral fluids without difficulty. In severe cases of tetanus it may be necessary to feed by gavage. However, as illustrated in the case presented, an attempt to pass a gavage tube into the stomach of a lightly sedated patient may initiate a succession of spasms, including laryngospasm. *Before passing a gavage tube, heavily sedate the patient.* In more severe cases undergoing frequent muscular spasms, it would be well to delay gavage feeding because of the danger of vomiting and aspiration. The patient may be kept hydrated and in fair protein and nutritional balance by the judicious use of electrolyte and dextrose solutions, albumin and blood and parenteral vitamins. Of course, the problem becomes one of fluid and electrolyte bal-

ance but this problem will not assume too great an importance if it exists for only a few days. As the spasms lessen in intensity, gavage feeding may be initiated.

A strict intake and output record must be kept to lessen the chance of under or over hydration. A urinary retention catheter should be inserted so as to facilitate urine output records. The patient with tetanic spasms will lose an excess amount of fluid in the perspiration and it will be necessary to take into account perspiration losses in the daily fluid replacement. Daily urines for microscopic analyses and specific gravity should be part of the therapeutic regime. While the patient remains on parenteral fluids as his only source of water and electrolytes, daily or every other day a blood electrolyte pattern should be determined. An occasional determination of the total protein values of the blood will guide the replacement of protein losses by whole blood or serum albumin.

SUMMARY

It will be obvious that the present-day successful treatment of a patient with tetanus represents one of the most severe challenges the physician may be called upon to face. The entire resources of the hospital must be called into play and a team consisting of a pediatrician, surgeon and anesthetist aided by a devoted and trained nursing staff should be set up and be made personally responsible for the patient's recovery. Eternal vigilance is necessary. At any time during the course of the disease a sudden complication will undo all the hard work that has gone before and the patient will be lost. Only by adhering to a definite yet flexible routine and by utilizing a large portion of the medical armamentarium will a successful outcome be assured.

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SALICYLATE INTOXICATION

Joseph M. Lo Presti, M.D.†

INTRODUCTION

The following case is deemed worthy of reporting because it affords the opportunity of discussing salicylate intoxication. It also points out the necessity of recognizing that excessive amounts of aspirin are often dangerous and may, on occasion, result in a fatal outcome.

CASE REPORT

J. T. F.,* A nine month old white male was admitted to the Children's Hospital on December 10, 1953. The history revealed that the infant was well until three days prior to admission when fever and persistent vomiting occurred. The emeses were postprandial, non-projectile, contained no bile, and consisted mainly of recently ingested food. A private physician was consulted who diagnosed an acute tonsillitis for which penicillin was administered. *In the 24 hour period before hospitalization, the mother had given the patient 30 aspirin tablets, a total of 37 grains.* On the morning of admission, the infant's repirations became rapid and labored and extreme paleness and lethargy appeared. Because of these new symptoms he was brought to the hospital. The remaining history was non-contributory.

The initial physical examination revealed a respiratory rate of 60 per minute, fever of 103 degrees (F), and a pulse rate of 100 per minute. The respirations were rapid and labored. The infant was pale and completely limp but responded to external stimuli. The pupils were constricted but reacted to light and accommodation. The mucous membranes were dry and an exudative tonsillitis was present. The remaining examination including the neurological was essentially normal.

The important laboratory findings were an alkaline urine which was strongly positive for salicylates and acetone. The spinal fluid was normal. The pH of the blood was 7.47 and the carbon dioxide combining power 21 volumes per cent (9.5 meq per liter). The prothrombin time was 30 per cent of normal and the blood chlorides 113 meq per liter. The blood salicylate level was 60 mgms. per cent.

The patient was placed in an oxygen tent and 280 milliliters of ⅙ molar sodium lactate was administered intravenously followed by 80 milliliters of fresh plasma and 180 milliliters of Butler's solution. Six hours after the lactate was given, the pH of the blood was 7.26 and the carbon dioxide combining power 25 volumes per cent (11.3 meq per liter) and there was no noticeable change in the physical condition. One-

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* Private patient of Joseph Rose, M.D.

sixth molar sodium lactate was again administered intravenously in a dose of 165 milliliters. Six hours later, the carbon dioxide combining power was 30 volumes per cent (13.5 meq per liter). The infant's condition worsened, cyanosis appeared, and death occurred 15 hours after admission to the hospital. An autopsy was not performed.

DISCUSSION

Aspirin is one of the most effective antipyretic drugs in medicine and it is used extensively. It is probable that more aspirin is ingested annually than any other drug. However, among both the medical population and the laity, it is not appreciated generally that aspirin is not an innocuous drug. Excessive ingestion may result in toxic blood levels and the serious clinical manifestations of salicylism. This fact is overlooked commonly and an educational campaign along these lines is in order.

ETIOLOGY

Aspirin is a much more toxic drug than is sodium salicylate and, therefore, is a more common cause of salicylate intoxication. Infants, particularly those under the age of one year, are more susceptible to the toxic effects of aspirin than are older children. The effective therapeutic dose of aspirin is one grain per year of age per dose up to the age of five years; after this period, the dose is five grains regardless of age. This amount may be given safely at four hour intervals. Under no circumstances should this dose be exceeded. The excessive administration of aspirin by physicians and parents is the cause of many instances of salicyism. The new popular sweetened aspirin tablets which flood the market are an added inducement to accidental ingestion and a relatively common cause of intoxication. Intoxication is encountered most frequently in rheumatic fever therapy where large doses of salicylate and near toxic blood levels are essential for beneficial effects.

CLINICAL FEATURES

Salicylate intoxication is a well-defined and easily recognizable clinical entity. If the index of suspicion is high and the condition is kept in mind, the diagnosis may be suspected and established easily. A searching history will elicit the excessive ingestion or administration of salicylate. It is an interesting sidelight that the author has encountered a number of instances of toxicity during the course of diseases which are attended by high fever, and of these, the most common has been measles. Anxious parents attempt to reduce the hyperpyrexia by giving excessive amounts of aspirin. In a short time the patient develops tachypnea which progresses rapidly to frank hyperpnea. This respiratory aberration is a constant feature and resembles exactly the hyperpnea of diabetic acidosis. Usually, the general appearance

of the patient is one of apathy and lassitude. Paradoxically, fever will be present and it may be excessively high. An undue amount of sweating will be noted and dehydration occurs rather rapidly. Abdominal pain may occur. Older patients may present the subjective symptoms of anorexia, tinnitus, thirst, and vertigo. Hemorrhagic phenomena may occur, particularly epistaxis. In the more severe intoxications there may be pallor, cyanosis, irritability, and restlessness. Central nervous system involvement may be manifested by disorientation, stupor, and convulsions.

LABORATORY FINDINGS

The laboratory findings are consistent and diagnostic. Both the prothrombin and coagulation times will be increased. Invariably, the blood chlorides are elevated. The urine may yield a reduction of copper by salicylate, a positive ferric chloride reaction for salicylates, the presence of ketone bodies, and there may be albumin, casts, leucocytes, and red blood cells. Salicylate blood levels usually will be in the toxic range, i.e., above 32–40 milligrams per cent. Initially, the blood pH will be elevated and the carbon dioxide combining power will be lowered (respiratory alkalosis). Later, both the pH of the blood and the carbon dioxide combining power are decreased (metabolic acidosis).

PATHOGENESIS

Many of the features of salicylism cannot be explained fully. The hemorrhagic phenomena, such as epistaxis and hematuria are due to a prolongation of the prothrombin time. That the hypoprothrombinemia is not a result of hepatic damage is evidenced by the fact that the parenteral administration of vitamin K corrects this deficit. There is some suggestive evidence that when dicumarol is administered to a patient, it is converted to salicylates. It has been postulated that these salicylates inhibit the formation of prothrombin by the liver and, thus, are responsible for the anticoagulant effect of dicumarol. The hypoprothrombinemia which accompanies salicylate intoxication would appear to support this hypothesis.

Early in salicylism a respiratory alkalosis is produced. A toxic blood level of salicylate directly stimulates the central nervous system and causes hyperpnea. The Henderson-Hesselbach equation states that the pH of the blood is directly proportional to the ratio of the concentrations of (HCO_3) to (CO_2) in the blood stream, i.e., pH (blood) = 6.1 log (HCO_3)/(CO_2) *at the normal blood pH of 7.4, this ratio is 20 to 1.* Hyperpnea produces a decrease in the concentration of carbon dioxide, i.e. carbon dioxide is "blown off" and, as a result, there is an increase in this normal 20 to 1 ratio. This is reflected in an elevation of the blood pH (respiratory alkalosis). When-

ever the ratio of the (HCO_3) to (CO_2) in the serum is altered, the body immediately calls into play mechanisms which are designed to return the ratio to 20 to 1. When these mechanisms have exerted their optimal effect, the condition is termed "compensated". It should be remembered that even under the most ideal situations "ratio repair" and "compensation" are never complete. One of the unique properties of the kidney is its ability to concentrate and preferentially excrete large amounts of bicarbonate. When the (CO_2) is decreased, "ratio repair" can be accomplished only by a concomitant decrease in (HCO_3). Thus, this renal mechanism becomes operative and large amounts of bicarbonate are excreted in the urine. At this stage, the urinary pH will be alkaline and this may be utilized as a test to differentiate early respiratory alkalosis from later metabolic acidosis.

The child with salicylism early and rapidly develops a metabolic acidosis. This is produced primarily by a ketosis. As ketone bodies accumulate in the blood stream, they further reduce the concentration of the already lowered bicarbonate. This proceeds to a stage where the ratio of (HCO_3) to (CO_2) is reduced *below* 20 to 1. An accompanying proportionate decrease in the blood pH occurs and the carbon dioxide combining power is depressed further. Ketosis is caused by a poisoning of the Kreb's cycle of carbohydrate metabolism by salicylate. Since carbohydrate metabolism ceases, caloric requirements are met by an increase in fat and protein metabolism. The liver converts fats into ketone bodies. These ketone bodies are then transported to muscle where complete metabolism takes place. There is a fixed rate at which muscle can handle ketone bodies and when this level is exceeded, ketonemia and ketonuria result. In salicylate intoxication, fat metabolism increases since carbohydrates cannot be utilized. The result is an excessive production of ketone bodies. The muscles cannot handle this extra load, and ketones appear in the blood and urine. The total effect is a lowering of the blood pH and the carbon dioxide combining power, resulting in metabolic acidosis. An additional factor is dehydration which has these effects:

1. The ability of muscle to metabolize ketone bodies is impaired;
2. Lactic acid accumulates and reduces further the concentration of bicarbonate;
3. Oliguria is produced which causes a retention of ketone bodies and lactic acid and exaggerates the acidemia.

At this time the urinary pH will be acid, a simple test for metabolic acidosis. To "repair" the lowered ratio of (HCO_3) to (CO_2), the body attempts to decrease the (CO_2) and thus the initial hyperpnea continues. There is evidence which suggests the exact point in the Kreb's cycle of carbohydrate metabolism where salicylate exerts its toxic action. It is a

well-established fact that the metabolic acidosis of salicylate intoxication is refractory to correction by parenterally administered ⅙ molar sodium lactate. In most cases large doses of lactate are necessary before a beneficial effect is produced; in a few instances lactate will have no effect, or the acidosis becomes more severe despite the administration of lactate. It would appear then that salicylate exerts its depressant action on carbohydrate metabolism by inhibiting the utilization of lactate.

Dehydration in salicylism probably is due to a combination of factors including 1) The exessive sweating, and 2) the fluid lost via the lungs as a result of hyperpnea. The central nervous system manifestations are probably produced by the direct neurotoxic action of salicylate. Fever, an invariable symptom, is probably the result of dehydration, toxicity, hemorrhage, and central nervous system involvement.

Methyl salicylate (oil of wintergreen) poisoning is the most severe form of salicylate intoxication and often terminates fatally. Most commonly it is ingested accidentally, and its pleasant peppermint odor increases the hazard of accidental ingestion. Its severity is due to the fact that, in addition to the toxic effects of salicylate, there is a *marked central depression* produced by the methyl radical.

TREATMENT

The possibility of hemorrhage should be a prime consideration in these patients. It has been noted that the hypoprothrombinemia can be corrected by the parenteral administration of vitamin K. Fresh human plasma is a readily available source of prothrombin and it may be given intravenously in an amount not to exceed 10 milliliters per pound of body weight. However, there are available effective, rapidly-acting vitamin K preparations, e.g., vitamin K_1-oxide. These may be given intramuscularly or intravenously in doses of 50 to 100 milligrams. This amount should be repeated at three hour intervals until the prothrombin time is normal.

The therapeutic implications of respiratory alkalosis versus metabolic acidosis are apparent. *Alkalinizing solutions are not to be administered during the early alkalotic phase of salicylism since they would serve only to increase the alkalosis.* In this situation the carbon dioxide combining power will not differentiate early alkalosis from the later acidosis since in either instance, this determination will be decreased. The pH of the urine is a practical and easy way of differentiating the two. It has been pointed out that the early phase of respiratory alkalosis is a transient one in children, and the change to metabolic acidosis is rapid. It occurs within 12 to 24 hours after ingestion and by the time treatment is started, acidosis already has appeared. This makes the difference an academic one and has little bearing on the therapy.

The most important phase of treatment is the correction of acidosis. This is accomplished by the intravenous administration of an appropriate alkalinizing solution. As indicated previously, ⅙ molar sodium lactate will prove to be disappointing unless it is given in large amounts. At the present time the best results will be obtained from the use of an isotonic solution of sodium bicarbonate, i.e., a 1.4 per cent solution of sodium bicarbonate may be administered intravenously with safety if it is dripped in slowly at a rate *not exceeding 8 to 10 drops per minute*. The objective is to attempt to raise the carbon dioxide combining power to about 40 volumes per cent. When a 1.4 per cent solution of sodium bicarbonate is given in an amount of 0.8 cubic milliliters per pound of body weight, it will raise the carbon dioxide combining power of the blood one volume per cent. From this is derived the formula:

(40 minus the patient's CO_2 combining power) $\times$ 0.8 $\times$ patient's wt. in lbs. = number of cubic milliliters of 1.4% $NaHCO_3$ to be given. A close check is kept on the carbon dioxide combining power and more bicarbonate is administered if the determination remains below 35 volumes per cent.

Dehydration should be corrected by the parenteral administration of fluids. In severe cases of intoxicaton, it probably is best to give fluids via the continuous intravenous drip method for the first 24 to 48 hours. The total daily fluid intake is calculated on a weight basis, and a total of 75 to 100 cubic milliliters of fluid per pound of body weight is given for each 24 hour period. The choice of fluid is dictated by well-defined principles of acid-base balance. A calculated amount of an alkalinizing fluid is given to correct the acidosis. As mentioned before, fresh plasma may be utilized in a dose of 10 cubic milliliters per pound of body weight, for both its protein and prothrombin content. The daily salt requirements should be met, i.e., 2 to 2.5 grams of salt per day. Butler's solution is best for this purpose since it supplies some potassium and calories in addition to sodium. Finally, large amounts of 5 per cent glucose in water are indicated, since glucose not only supplies calories but also enhances the excretion of salicylate.

Oxygen therapy is not an essential feature but in the presence of cyanosis and marked hyperpnea its use probably is indicated.

In methyl salicylate poisoning, the central depression should be combatted by the use of central stimulants, (i.e., caffeine, coramine, etc.) artificial aids to respiration and oxygen therapy.

SUMMARY

A case of severe salicylate intoxication with a fatal termination has been presented. The etiology, laboratory findings, pathogenesis, and treatment of salicylism have been discussed.

CLINICO-PATHOLOGICAL CONFERENCE

Directed By: E. Clarence Rice, M.D.
Assisted By: Jerome Bernstein, M.D.
By Invitation: Morris I. Michael, M.D.

J. D., a two month old colored male, was admitted to the hospital January 25, 1945 because of jaundice of two weeks duration.

The patient was apparently in good health until two weeks prior to admission when he developed yellowish discoloration of the sclerae and skin, dark yellow urine, and cream colored stools. His appetite remained good and there had been no vomiting, diarrhea, constipation or neurological symptoms.

The child was born at full term weighing 8¾ lb. This was the first born child of these parents. The possibility of inadequately treated syphilis existed in both parents.

Physical examination on admission revealed a well developed, well nourished colored male in no distress. The temperature, which was 101°, returned to normal in a few hours. The skin showed moderate jaundice. There was an abundance of hair and a large anterior fontanelle. The sagittal suture was open and was one centimeter in width. The ears, nose, mouth and pharynx were normal. The sclerae were moderately jaundiced. The heart and lungs were normal. The abdomen was soft and there was a small umbilical hernia. The liver edge was palpable one fingerbreadth below the right costal margin, but apparently was non-tender. The reflexes were hyperactive.

The bleeding and coagulation times were normal. The serology was negative. The laboratory findings are summarized in the chart.

The patient's condition remained unchanged; jaundice, light colored stools, and good appetite persisted. On the twelfth hospital day the temperature rose to 101° and he developed diarrhea. Without specific therapy the temperature returned to normal and the diarrhea subsided in one week.

On the twenty-first hospital day an exploratory laparotomy was performed. A small finger-like pouch which had the color and appearance of small bowel was found at the site of the gallbladder. On aspiration a small amount of bile was found. The biliary, cystic, and common bile ducts were reported as normal. No obstruction in the biliary system could be found. A cholecysto–duodenostomy was performed. The post-operative condition was fair. On the following day, the patient's temperature rose to 104°, but physical examination revealed no significant findings. Two days later the wound seemed to be healing, but bile was oozing onto the dressing. Bile was still present in the urine and the temperature was still spiking to 104°. On February 19, four days post-operative, the sutures loosened and evisceration of the wound occurred. The abdomen became distended and tense. Under local anesthesia five wire stays were inserted. The patient was given sulfadiazine and penicillin. The same day it was noted that the infant had not voided for about 18 hours. Catheterization yielded only a few drops of very thick, dark, yellow urine. The temperature remained high. Levine and rectal tubes, and prostigmine offered no relief. The patient died the following day, the sixth post-operative day and the twenty-seventh hospital day.

Morris I. Michael, M.D.

We have here a two months old colored male with the chief complaint of painless jaundice, some intermittent fever and diarrhea, in whom obstructive jaundice was chemically suspected, who came to surgery without an

Date	Urine							Blood							Stool
	React.	Sp. Gr.	Alb. mg./ 400 ml.	Sugar	Acet.	Micro	Bile	Hgb gm./100 ml.	WBC	Poly.	Lymph.	Eosin.	Icteric index units	Total bilirubin mg./100 ml.	Pro-thrombin time	Bile
1/26/45	Acid	QNS	5	0	0	Occ. RBC		12	9300	29	65	6				
1/27													135	Immed. dir. 9.2		Faintly positive
2/1	Acid	QNS	0	0	0	Occ. WBC									97% Norm. act.	
2/2							+									Neg. 2 exam.
2/4													8.5	5.0		
2/7	Acid	QNS	200	0	0	Many WBC	+									
2/8	Alk	QNS	30	0	0	Few WBC	+									
2/9	Acid	QNS	20	0	0	Few WBC	+									
2/10																Negative
2/14	Acid	QNS	70	0	0	Few WBC	+	12.5	6800	25	71	4				
2/18							+	16.5								
2/20									11800	74	25					
2/21							+						279			

obvious obstruction being found, yet an anastomosis of the gallbladder and duodenum was performed. Post-operative complications, dehiscence of the wound, evisceration, urinary infection and anuria eventually resulted in death.

In this case we are obviously faced with the differential diagnosis of jaundice. We must decide first of all whether our problem fits into the category of retention jaundice, in which the liver is unable to remove the breakdown products of blood, such as in hemolytic anemia, or regurgitation jaundice where there is return of bile from the liver to the blood stream because of obstruction somewhere within or without the biliary system.

The laboratory findings of an immediate direct van den Bergh, almost complete absence of bile in the stool, and the presence of bile in the urine all point to an obstructive jaundice in which the bilirubin in the blood is not bound to protein because the regurgitated bile salts prevent this combination.

Now we need only find the particular etiology for this obstructive jaundice to have our final diagnosis.

Jaundice in the newborn period may either be early or late. If early, as in physiological jaundice or erythroblastosis we would expect retention jaundice, indirect van den Bergh, absence of bile from the urine, etc. We can conceive, however, of plugs of bilirubin as seen in erythroblastosis or familial hemolytic jaundice plugging the liver canaliculi so as to cause a secondary, late regurgitation type jaundice.

Here, however, we have jaundice late in the newborn period characteristic of congenital atresia of the bile ducts, syphilitic cirrhosis, calculi, choledochal cyst or post-infectious portal cirrhosis. Syphilis, although suggested by the family history, seems ruled out by the negative serology and the absence of confirmatory signs as seen in the skin and the skeletal system.

A commonly missed cause of Banti's syndrome or portal hypertension, is infection of the umbilicus, which travels up the umbilical vein causing portal thrombosis and eventually portal cirrhosis. This is a process which should take years in the pathogenesis, so we must look more to congenital malformations in our case.

Our surgeon apparently found a gallbladder of sorts, and normal biliary (hepatic) cystic and common bile ducts. Bile was found in this apparently atypical gallbladder and later was found oozing onto the dressings. Hence the only area of congenital malformation and obstruction not directly visualized by the surgeon would be in the intra-hepatic ducts, a commonly recognized form of biliary atresia.

Presumably he could have missed scar tissue about the portal veins with portal hypertension or a fetal portal cirrhosis, or failed to find evidence of hepatic damage from a hemolytic antibody in erythroblastosis, or septi-

cemia, but he could scarcely have failed to see a choledochal cyst, or neoplasm causing external obstruction to the free flow of bile. Moreover the almost benign preoperative course, good nutrition and absence of toxicity seem to rule against a generalized infection or septicemia.

To return then to congenital atresia of the intra-hepatic ducts. Here we might also hypothecate the presence of cystic disease of the liver which arises from partially canalized bile ducts, and which is associated frequently with polycystic disease of the kidneys. This might explain the secondary kidney failure in our patient which played so evident a part in his post-operative demise.

My diagnosis then is congenital biliary atresia of the intra-hepatic ducts, with or without cystic disease of the liver and of the kidney.

Jerome Bernstein, M.D.

The body was that of a well developed and fairly well nourished, dehydrated colored male, weighing 4.7 kg., body length 61 cm. There was marked icterus of the skin and mucous membranes. The thoracic viscera were normal. The peritoneal cavity was free of fluid. The liver weighed 160 gm., the normal being 140 gm. The lower border was flush with the costal margin. The tissue was firm and cut with resistance revealing a finely lobulated surface. The gall bladder had been anastamosed to the duodenum and when the former was opened it was found to contain some duodenal contents. The main biliary ducts were atretic. The spleen was normal. A partial obstruction of the middle third of the ileum due to a congenital stricture was present. The bowel above this point was markedly dilated, that below being small and collapsed. The mucosa at the constriction was pale and atrophic. The entire gut was yellow in color. The examination of the other viscera revealed nothing abnormal.

MICROSCOPIC EXAMINATION OF TISSUES

Many of the alveoli of the lungs are filled with edema fluid, most of the bronchioles being collapsed. Only a few air bearing areas are noted.

The liver cells have lost their normal arrangement and appearance. Many large multinucleated cells are placed in an irregular arrangement, interspersed with many smaller parenchymal cells, some containing fat. Interspersed between the groups of parenchymal cells are many round cells, some polymorphonuclear leucocytes and phagocytic cells laden with bile pigment. Variable numbers of fibroblasts are present. The arrangement of the structures making up the trinities is considerably disturbed and it is with difficulty that the bile ducts can be identified. They are not increased in number.

The pancreas is normal. The spleen is congested and the Malpighian

corpuscles are reduced in size. In the kidney the cells lining the convoluted tubules are swollen and bile stained, often occluding their lumens, some of their nuclei having disappeared. A number of the tubules are dilated. Some of the degenerating epithelial cells of the convoluted tubules are surrounded by a ring of black pigment. The adrenal medullae are markedly congested. The tissues from other organs showed nothing remarkable.

The pathological diagnosis at the time of necropsy, which was nine years ago (1945) was:

1. Icterus.
2. Congenital stenosis of the bile ducts with biliary cirrhosis.
3. Stenosis of the ileum with partial obstruction.
4. Pulmonary edema.
5. Post cholecysto-duodenostomy.

E. Clarence Rice, M.D.

Subsequent to this (1949), we were informed by Dr. Roland B. Scott of Freedman's Hospital that a two months old brother of this patient had been admitted with similar symptoms and findings to our patient. This jaundiced baby was also subjected to laparotomy. The gall bladder and bile ducts were reported as being normal. Death occurred eight days after the operation.

Three years later (1952), the six months old sister of these children was admitted to Freedman's Hospital, having been jaundiced for two months prior to admission. One month after admission this patient was operated upon and a normal biliary tract was demonstrated, this being confirmed by x-ray examination by the use of lipiodol. Fifty-one days later a cholecysto-duodenostomy was performed. The patient died the following day.

Sections of the livers of the three patients were submitted to Dr. Sidney Farber, pathologist at Children's Hospital, Boston, by Dr. Scott. Dr. Farber interpreted the findings in all of the specimens to be due to viral hepatitis.

It is interesting that the diagnosis of viral hepatitis was never considered by us, and it was only after the physicians at Freedman's Hospital had seen two siblings with almost identical findings, that the diagnosis of viral hepatitis was entertained.

The family of these patients was investigated by Dr. Scott and his associates, and the parents and two living siblings were apparently in good health. The mother stated that she had been well during her pregnancies and that neither she nor the two living children had ever been jaundiced. These three individuals had positive cephalin flocculation tests. The thymol

turbidity tests were negative and the alkaline phosphatase were 1.14, 9.35, and 10.54 units per 100 ml., for the mother, brother and sister respectively.

Drs. Scott, Wilkins and Kessler (1) have reported these three patients. The autopsies show liver pathology which is consistent with the findings which are seen in viral hepatitis. They report laboratory findings in the mother and two living siblings which they consider to be evidence of liver damage.

This case has been a most informative one for us. The subsequent information supplied by Dr. Scott and his associates makes us cognizant of the role played by viral infections in the newborn. Our original concept of this patient's illness, viz., stenosis of the bile ducts with biliary atresia, is no longer tenable in the light of the subsequent histories of the other members of the patient's family. Viral hepatitis has been said to be milder in childhood than in later years. It would appear that in the newborn the disease pursues a more fulminating course and that its effects are more likely to result in death than in those of other age groups. Certainly an increased awareness of the present concepts of jaundice will aid us in recognizing such an illness as we have discussed today for what it really is.

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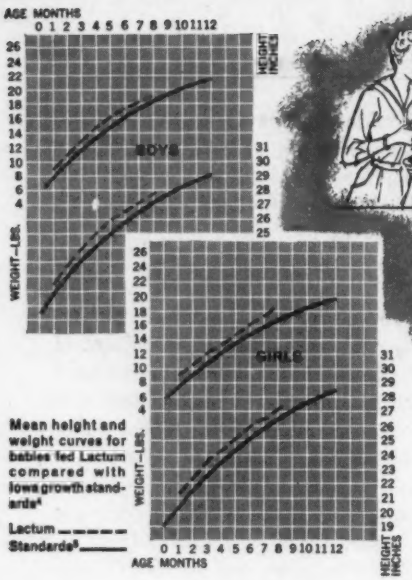

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